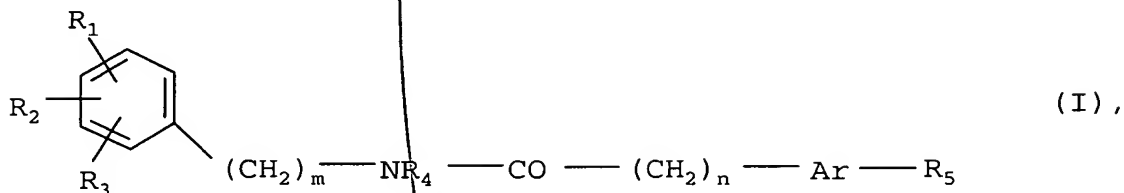


Patent Claims

1. Carboxylic acid amides of general formula



wherein

one of the groups m or n denotes the number 0 and the other group m or n denotes the number 1,

Ar denotes a phenylene or naphthylene group optionally substituted by a fluorine, chlorine or bromine atom, by a trifluoromethyl, C<sub>1-3</sub>-alkyl, hydroxy, C<sub>1-3</sub>-alkoxy, phenyl-C<sub>1-3</sub>-alkoxy, amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group, whilst the phenylene group may be substituted by another fluorine, chlorine or bromine atom or by another C<sub>1-3</sub>-alkyl group,

a thienylene, thiazolylen, pyridinylen, pyrimidinylene, pyrazinylen or pyridazinylene group optionally substituted in the carbon skeleton by a C<sub>1-3</sub>-alkyl group,

R<sub>1</sub> denotes a C<sub>1-3</sub>-alkyl group optionally substituted by an amino, C<sub>1-3</sub>-alkylamino, di-(C<sub>1-3</sub>-alkyl)-amino, phenyl, naphthyl, heteroaryl or 4- to 7-membered cycloalkyleneimino group,

a C<sub>3-7</sub>-cycloalkyl group which is substituted in the 1 position by a 5- to 7-membered cycloalkyleneiminocarbonyl group,

an amino, C<sub>1-5</sub>-alkylamino, C<sub>5-7</sub>-cycloalkylamino or phenyl-C<sub>1-3</sub>-alkylamino group which may in each case be substituted at the amino-nitrogen atom by a benzoyl or phenylsulphonyl

group or by a C<sub>1-3</sub>-alkyl or C<sub>1-3</sub>-alkylcarbonyl group optionally substituted in the C<sub>1-3</sub>-alkyl moiety by a carboxy group,

a 4- to 7-membered cycloalkyleneiminocarbonyl or cycloalkyleneiminosulphonyl group optionally substituted by a C<sub>1-3</sub>-alkyl group,

an aminosulphonyl group optionally substituted by one or two C<sub>1-3</sub>-alkyl groups,

a phenyl group optionally substituted by a fluorine, chlorine or bromine atom, by a trifluoromethyl, aminosulphonyl, C<sub>1-3</sub>-alkyl or C<sub>1-3</sub>-alkoxy group, which may additionally be substituted by a fluorine, chlorine or bromine atom or by a trifluoromethyl, C<sub>1-3</sub>-alkyl or C<sub>1-3</sub>-alkoxy group,

a C<sub>1-3</sub>-alkoxy, phenyl-C<sub>1-3</sub>-alkoxy, heteroaryloxy or heteroaryloxy-C<sub>1-3</sub>-alkoxy group wherein the alkoxy moiety may be substituted in the 2 or 3 position in each case by an amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group,

a C<sub>3-7</sub>-cycloalkoxy group, whilst the methylene group in the 3 or 4 position in a C<sub>5-7</sub>-cycloalkoxy group may be replaced by an -NH group, whilst the -NH group may be substituted

by a C<sub>1-3</sub>-alkyl group which may be substituted in the 2 or 3 position by an amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group, by a C<sub>1-3</sub>-alkylcarbonyl, arylcarbonyl or arylsulphonyl group or

by an aminocarbonyl, C<sub>1-3</sub>-alkylaminocarbonyl or di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl group, wherein in each case the oxygen atom of the carbonyl group is replaced by an imino group,

$R_2$  denotes a hydrogen, fluorine, chlorine or bromine atom, a  $C_{1-3}$ -alkyl, hydroxy or  $C_{1-3}$ -alkoxy group,

$R_3$  denotes a hydrogen atom or a  $C_{1-3}$ -alkyl group,

$R_4$  denotes a hydrogen atom or a  $C_{1-3}$ -alkyl group optionally substituted by a carboxy group and

$R_5$  denotes a cyano group or an amidino group optionally substituted by one or two  $C_{1-3}$ -alkyl groups, whilst

by the abovementioned heteroaryl groups is meant a 5-membered heteroaryl group optionally substituted by a  $C_{1-3}$ -alkyl group which contains, in the heteroaromatic moiety,

an imino group optionally substituted by a  $C_{1-3}$ -alkyl group, or an oxygen or sulphur atom,

an imino group optionally substituted by a  $C_{1-3}$ -alkyl group and an oxygen, sulphur or nitrogen atom,

an imino group optionally substituted by a  $C_{1-3}$ -alkyl group and two nitrogen atoms or

an oxygen or sulphur atom and two nitrogen atoms,

or a 6-membered heteroarylene group optionally substituted by a  $C_{1-3}$ -alkyl group which contains one or two nitrogen atoms in the heteroaromatic moiety,

the carboxy groups mentioned in the definition of the abovementioned groups may be replaced by a group which may be converted into a carboxy group *in vivo* or by a group which is negatively charged under physiological conditions or

the amino and imino groups mentioned in the definition of the abovementioned groups may be replaced by a group which may be cleaved *in vivo*,

the isomers and salts thereof.

2. Compounds of general formula I according to claim 1, wherein

one of the groups m or n denotes the number 0 and the other group m or n denotes the number 1,

Ar denotes a phenylene group optionally substituted by a fluorine, chlorine or bromine atom or by a methyl, hydroxy, methoxy or benzyloxy group, which may be substituted by another methyl group,

R<sub>1</sub> denotes a phenyl group optionally substituted by a fluorine, chlorine or bromine atom or by a trifluoromethyl, aminosulphonyl, C<sub>1-3</sub>-alkyl or C<sub>1-3</sub>-alkoxy group, which may additionally be substituted by a fluorine, chlorine or bromine atom or by a trifluoromethyl, C<sub>1-3</sub>-alkyl or C<sub>1-3</sub>-alkoxy group,

a methyl group substituted by a dimethylamino, pyrrolidino or imidazolyl group, wherein the imidazolyl moiety may be substituted by a methyl group,

an amino, C<sub>1-5</sub>-alkylamino, cyclopentylamino or benzylamino group which may be substituted at the amino-nitrogen atom by a carboxy-C<sub>1-2</sub>-alkyl, C<sub>1-3</sub>-alkoxycarbonyl-C<sub>1-2</sub>-alkyl, carboxy-C<sub>1-2</sub>-alkylcarbonyl or C<sub>1-3</sub>-alkoxycarbonyl-C<sub>1-2</sub>-alkylcarbonyl group,

a benzoylamino or phenylsulphonylamino group,

a cyclopropyl group (which is substituted in the 1 position by a 5- to 7-membered cycloalkyleneiminocarbonyl group,

an optionally methyl-substituted pyrrolidinocarbonyl, piperidinocarbonyl, pyrrolidinosulphonyl or piperidinosulphonyl group,

a C<sub>1-3</sub>-alkoxy group wherein the alkoxy moiety in the 2 or 3 position may be substituted in each case by an amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group,

a phenyl-C<sub>1-3</sub>-alkoxy or pyridinyloxy group,

a C<sub>5-7</sub>-cycloalkoxy group wherein the methylene group in the 3 or 4 position may be replaced by an -NH group, whilst the -NH group may be substituted

by a C<sub>1-3</sub>-alkyl or C<sub>2-3</sub>-alkanoyl group,

by a C<sub>2-3</sub>-alkanoyl or aminocarbonyl group wherein in each case the oxygen atom of the carbonyl group is replaced by an imino group,

R<sub>2</sub> denotes a hydrogen, fluorine, chlorine or bromine atom, a methyl, hydroxy or methoxy group,

R<sub>3</sub> denotes a hydrogen atom or a methyl group,

R<sub>4</sub> denotes a hydrogen atom or a methyl or ethyl group optionally substituted by a carboxy or C<sub>1-3</sub>-alkoxycarbonyl group and

R<sub>5</sub> denotes a cyano group or an amidino group optionally substituted by a C<sub>1-6</sub>-alkoxycarbonyl or benzoyl group,

the isomers thereof and the salts thereof.

3. Compounds of general formula I according to claim 1, wherein

one of the groups m or n denotes the number 0 and the other group m or n denotes the number 1,

Ar denotes a phenylene group optionally substituted by a methyl, hydroxy, methoxy or benzyloxy group,

Al  
R<sub>1</sub> denotes a phenyl group optionally substituted by a fluorine, chlorine or bromine atom or by a trifluoromethyl, aminosulphonyl, C<sub>1-3</sub>-alkyl or C<sub>1-3</sub>-alkoxy group, which may additionally be substituted by a fluorine, chlorine or bromine atom or by a trifluoromethyl, C<sub>1-3</sub>-alkyl or C<sub>1-3</sub>-alkoxy group,

a cyclopropyl group which is substituted in the 1 position by a 5- to 7-membered cycloalkyleneiminocarbonyl group, or a 4- to 7-membered cycloalkyleneiminocarbonyl group,

an optionally methyl-substituted pyrrolidinocarbonyl, piperidinocarbonyl or pyrrolidinosulphonyl group,

R<sub>2</sub> denotes a hydrogen, fluorine, chlorine or bromine atom or a methyl group,

R<sub>3</sub> denotes a hydrogen atom or a methyl group,

R<sub>4</sub> denotes a hydrogen atom or a methyl or ethyl group substituted by a carboxy, methoxycarbonyl or ethoxycarbonyl group and

R<sub>5</sub> denotes an amidino group optionally substituted by a C<sub>1-6</sub>-alkoxycarbonyl or benzoyl group,

the isomers thereof and the salts thereof.

4. The following compounds of general formula I according to claim 1:

(a) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide,

(b) 2-(2-benzyloxy-5-carbamimidoyl-phenyl)-N-(2-ethoxycarbonyl-ethyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide,

(c) 2-(2-hydroxy-5-carbamimidoyl-phenyl)-N-(2-ethoxycarbonyl-ethyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide,

(d) 2-(2-hydroxy-5-carbamimidoyl-phenyl)-N-(2-carboxy-ethyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide,

(e) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(piperidin-1-yl-carbonyl)-phenyl]-acetamide and

(f) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(2-aminosulphonyl-phenyl)-phenyl]-acetamide,

wherein the amidino group may additionally be substituted by a C<sub>1-6</sub>-alkoxycarbonyl or benzoyl group, and the salts thereof.

5. 2-(5-Carbamidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide and the salts thereof.

6. Physiologically acceptable salts of the compounds according to claims 1 to 5 wherein R<sub>5</sub> denotes one of the amidino groups mentioned in claims 1 to 5.

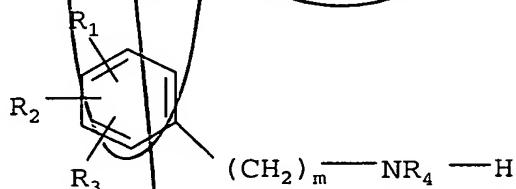
7. Pharmaceutical compositions containing a compound according to at least one of claims 1 to 5, wherein  $R_5$  denotes one of the amidino groups mentioned in claims 1 to 5, or a salt according to claim 6 optionally together with one or more inert carriers and/or diluents.

8. Use of a compound according to at least one of claims 1 to 5, wherein  $R_5$  denotes one of the amidino groups mentioned in claims 1 to 5, or a salt according to claim 6, for preparing a pharmaceutical composition having an anti-thrombotic activity.

9. Process for preparing a pharmaceutical composition according to claim 7, characterised in that a compound according to at least one of claims 1 to 5, wherein  $R_5$  denotes one of the amidino groups mentioned in claims 1 to 5, or a salt according to claim 6 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

10. Process for preparing the compounds according to claims 1 to 6, characterised in that

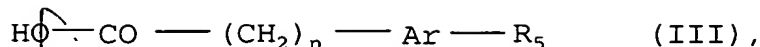
a) a compound of general formula



wherein

$R_1$  to  $R_4$  and  $m$  are defined as in claims 1 to 5, is acylated with a carboxylic acid of general formula

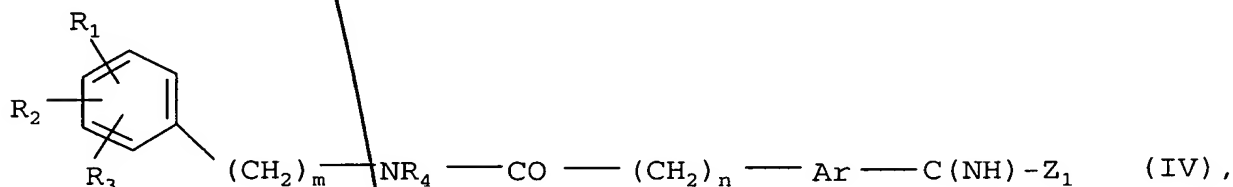




wherein

Ar, R<sub>5</sub> and n are defined as in claims 1 to 5, or with the reactive derivatives thereof, or

b) in order to prepare a compound of general formula I wherein R<sub>5</sub> denotes an amidino group which may be substituted by one or two C<sub>1-3</sub>-alkyl groups, a compound of general formula



optionally formed in the reaction mixture, wherein

R<sub>1</sub> to R<sub>4</sub>, Ar and n are defined as in claims 1 to 5 and Z<sub>1</sub> denotes an alkoxy, aralkoxy, alkylthio or aralkylthio group, is reacted with an amine of general formula



wherein

R<sub>6</sub> and R<sub>7</sub>, which may be identical or different, each denote a hydrogen atom or a C<sub>1-3</sub>-alkyl group, or with the salts thereof, and

subsequently, if desired, a compound of general formula I thus obtained which contains an amino or imino group is converted by means of a corresponding acyl derivative into a corresponding acyl compound of general formula I and/or

a compound of general formula I thus obtained which contains an esterified carboxy group is converted by hydrolysis into a corresponding carboxylic acid of general formula I and/or

a compound of general formula I thus obtained which contains a carboxy group is converted by esterification into a corresponding ester and/or

a protecting group used to protect reactive groups during the reactions is cleaved and/or

a compound of general formula I thus obtained is resolved into the stereoisomers thereof, and/or

a compound of general formula I thus obtained is converted into the salts thereof, particularly, for pharmaceutical use, into the physiologically acceptable salts thereof with an inorganic or organic acid or base.

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